## REMARKS

Claims 23-27 remain in this application. Claims 12-22 have been canceled by this amendment.

In the Claims

New claims 25-27 have been added. No new matter is added through this amendment. Support for claim 25 can be found on page 15, lines 14-15 of the specification as filed. Support for claims 26-27 can be found in Example 1, page 18 through page 20.

35 U.S.C§ 112

The Examiner has rejected claims 23-24 under 35 U.S.C§ 112 for lack of enabling disclosure. The Examiner has based the rejection on his opinion that at the time of the effective filing date of the present invention, "gene therapy was an immature and highly unpredictable art". The Examiner cites several references purported to indicate the imprecise nature of gene therapy at the time of filing.

Applicant respectfully points out that the standard for enablement under 35 U.S.C. §112 is that the specification fully enables one skilled in the art to make and use the invention without undue experimentation. As argued below, the Applicant submits that the specification, taken in conjunction with the state of the art at the time the invention was filed, (October 31, 1994) fully enabled the skilled artisan to make and use the invention.

Again, the Applicant respectfully refers to an article cited in the response dated March 5, 2001, which describes the successful use of ocular gene therapy. See Bennett et al., *Photoreceptor cell rescue in retinal degeneration (rd) mice by in vivo gene therapy*, Nature Medicine 2(6):649-654 (1996), previously submitted with the response filed October 9, 1999 in the parent case, cited in the IDS filed May 7, 2001 in the present application as reference 24 on form 1449. While the Examiner stated that all previously submitted arguments are not applicable to the present claims, he has again questioned the enablement of the invention based on the state of the art of gene therapy at the time of filing the present invention. Applicant respectfully submits that such arguments as presented previously that discuss the state of gene therapy are applicable to claims 23 and 24. Additionally, the Applicant points

out that Bennett et al. is not being used to supplement the disclosure of the application; rather, these reference is presented to show that the utility asserted and shown in the application is supported by further research, and that the specification fully enables therapeutic use of ocular gene therapy. See In re Wilson, 135 USPQ 442, 444 (CCPA 1962); Ex parte Obukowicz, 27 USPQ 2d 1063 (BPAI 1993); Gould v. Quigg, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> "it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative."

Bennett et al. describes the successful gene therapy of rd mice using techniques significantly similar to the techniques outlined in the specification. Bennett et al. use a recombinant adenovirus containing the ßPDE (the rod photoreceptor specific cGMP phosphodiesterase gene), under control of the cytomegalovirus (CMV) promoter. The ßPDE gene replaces the E1 and the majority of the E3 region of a type 5 adenovirus (Ad5). $1 \times 10^8$ plaque-forming units (pfu) were injected into the subretinal space of rd mouse eyes. (See page 649, first full paragraph of second column). The presence of the ßPDE gene resulted in the formation of rows of photoreceptor nuclei with delays in photoreceptor cell death, while control mice had virtually no nuclei and significant cell death. The authors conclude that "the findings demonstrate cell rescue by in vivo gene transfer, thus supporting the feasibility of treating an inherited retinal degeneration by somatic gene therapy" (see last sentence of abstract on page 649).

As the Examiner will appreciate, this system is very similar to the systems described in the application. Adenoviral vectors are described, both in the examples and on page 14, lines 21-27. In fact, the examples use the CMV promoter as well, in an Ad5 adenovirus which has the CMV/ß- gal construction in place of the E1 region. $2 \times 10^6$ pfu was applied in several ways, as described in the Examples.

Thus, Bennett et al. validates the teachings of the specification, by showing that the specification does indeed provide "therapeutic benefit" as the Examiner requests.

The Examiner cites a number of references, most notably the Orkin report, to support his contention that "gene therapy was an immature and highly unpredictable art" at the time of effective filing date of the present invention. Specifically, the Examiner points out

passages in the cited references that call into question the efficiency of gene transfer protocols. However, the appellant respectfully points out that "efficiency", i.e. efficient delivery of genes using ideal vectors, is not required for patentability. It is true that the wide-spread commercial exploitation of gene therapy may require further developmental work; however, this is not the standard of patentability. The standard for 35 U.S.C. §112 enablement is that one skilled in the art can make and use the invention without undue experimentation. The Bennett et al. reference shows that the techniques outlined in the specification are sufficient to enable one skilled in the art to do so.

The Examiner's attention is respectfully drawn to M.P.E.P. §2164.04:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . A specification disclosure which contains a teaching of the manner and process of making an using an invention which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

As stated by the court in In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. (Emphasis added).

The appellant respectfully submits that the Examiner has not met this burden. Even assuming, arguendo, that the Examiner has made a *prima facie* case, the appellant has rebutted this case with the Bennett article.

The references cited by the Examiner are generally quite positive about the prospects of gene therapy, but point out some of the hurdles which may need addressing prior to the wide-spread use of gene therapy for any and all diseases, at least therapeutically. The Applicant points out that commercial exploitation of gene therapy requires many different considerations than the patenting of gene therapy techniques; the standards are quite different. Certainly the Examiner will appreciate that a new protein may be patentable

although methods for its large scale production, sufficient to allow its wide-spread use, have not been developed.

Additionally, the Applicant respectfully notes that the references cited by the Examiner in the pending Office Action discuss the difficulties associated with the attempt to find **generalized** gene therapy techniques. While gene therapy taken as a whole at the time of filing may have been immature, the present invention should not be presumed non-enabled simply because of its association with an imprecise art. The Applicant does not purport to enable all fields of gene therapy, merely the claimed invention related to gene therapy for ocular tissues.

The Examiner also is of the opinion that the specification does not provide adequate guidance for methods of treating an ocular wound by directly contacting an exogenous nucleic acid and an ocular cell *in situ*. The Applicant submits that the methods outlined in the specification, including direct application and injection into the eye, are suitable for direct delivery of the vectors per the claimed invention.

The Examiner further asserts that modulating the wound healing process to attain beneficial therapeutic effect is not routine and guidance in the specification is limited to teaching the use of TGF-β. The Examiner is also concerned that there is no teaching regarding the use of TGF- β as a "master therapeutic". The Examiner relies on Cordeiro, et al for the proposition that ocular wound healing is a complex event. The Applicant respectfully points out that while Corderio discusses the intricacies of ocular wound healing, it also discusses the potential usefulness of gene therapy in promoting ocular wound healing.

In response to the Examiner's statement that there is no evidence of the at the time of filing that TGF-β could be used successfully in the treatment of ocular wounds, the Applicant submits a set of references that discuss the use of TGF-β protein for the treatment of wounds in general and in the treatment of ocular wounds and diseases. These references illustrate that it was known in the art that administration of TGF-β to various types of wounds accelerates the wound healing response, generally, and in the eye, specifically. Roberts, et al., *Transforming growth factor type β: Rapid induction of fibrosis and angiogenesis in vivo and stimulation of collagen formation in vitro,* Proc. Natl. Acad. Sci. USA, 83:4167-4171 (1986) at page 4170; Massague, *The transforming growth factor-β family,* Annu. Rev. Cell. Biol. 6:597-641 (1990) at pages 616-617; Smiddy, et al., *Transforming growth factorβ, a biological chorioretinal glue,* Arch Ophthalmol., 107:577-580 (1989) and Glaser, et al.,

*Transforming growth factor-β2 for the treatment of full-thickness macular holes,* Ophthalmology, 99:1162-1473 (1992) (copies of which are enclosed as Exhibits E-H and are also submitted in the accompanying Information Disclosure Statement).

Additionally, the specification sets forth a road map for practicing the invention. For example, conditions used for the cellular uptake of specific forms of exogenous nucleic acids are disclosed. Specification pg. 11, lines 5 –16. The specification directs the use of these general viral techniques when using viral exogenous nucleic acids to facilitate gene therapy of the *in situ* ocular cells. Similarly, the methods of permitting entry of plasmids into a cell were generally known to those of skill in the art and the specification so directs the use of these methods to permit entry of plasmid exogenous nucleic acid to facilitate gene therapy of the *in situ* ocular cells. The specification has further discussions regarding specific conditions for the uptake of various exogenous nucleic acids on page 12, lines 24-31 through page 13, lines 1-3.

The specification further describes conditions permissive for the uptake of the exogenous nucleic acid specific to the cells of the eye. Specification page 12, lines 7-23. The specification states that conditions well known to those of skill in the art that relate to *in vitro* uptake can be applied to *in vivo* ocular cells. The specification then provides specific methods that may be particularly applicable to ocular cells on page 12 lines 13-18.

Importantly, the specification on page 12, lines 19-23, provides methods of determining when the nucleic acid has been successful taken up by the cell. The Applicant respectfully points out again that under *In re Wands* some experimentation is permissible. The specification provides the direction necessary to guide one of skill in the art to perform the invention with no undue experimentation.

The examples in the specification provide further guidance for determining conditions permissive for the direct uptake of exogenous nucleic acid in ocular cells. Example 1, page 20 lines 1-32, is particularly relevant as this section discusses surgical injury inflicted on a rat's eye and the successful introduction of exogenous nucleic acid into that injury. After direct introduction of the exogenous nucleic acid to the injury, the exogenous nucleic acid was taken up by and expressed protein in the *in situ* ocular cells.

The Applicant respectfully disagrees with the Examiner that claims 23-24 are not enabled for the breadth of their scope. The specification provides support for the introduction of exogenous nucleic acid into many types of ocular cells including corneal epithelial cells,

corneal endothethial cells, cells of the trabecular meshwork, choroids cells, retina, sclera or ciliary body cells, cells of the retinal or ocular vasculature, cells of the vitreous body or cells of the lens. Specification page 15, line 32, through page 17, line 12. While the specification does not provide examples for each cell type, as discussed above the specification provides the guidance necessary to allow determination of conditions permissive to the uptake of exogenous nucleic acid.

## CONCLUSION

In view of the foregoing, Applicant submits that claims 23-27 are in condition for allowance. Therefore, issuance of a formal Notice of Allowance is respectfully requested.

If, upon review, the Examiner feels there are additional outstanding issues which may be resolved by telephone, the Examiner is invited to call the undersigned attorney at (415) 781-1989

Respectfully submitted,

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Filed Under 37 CFR § 1.34(a)

Dated: May 5, 2003

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